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## COMMUNICATION

## A simple chemical model for clathrate hydrate inhibition by polyvinylcaprolactam†

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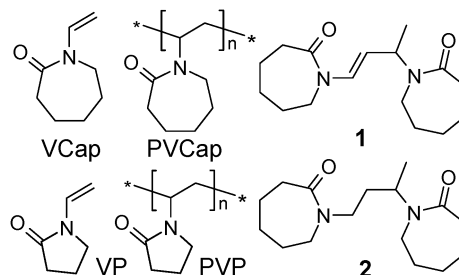
**A dimeric model compound gives structural insight into the mode of interaction of low dosage hydrate inhibitors with water.**

Gas clathrate hydrates present a very real challenge to the petrochemical industry, because in uninhibited systems they can agglomerate to form plugs within transport pipelines with consequent severe financial and safety implications.<sup>1</sup> This problem is increasingly successfully obviated using kinetic hydrate inhibitors (KHIs) which inhibit clathrate hydrate formation at concentrations as low as 0.5 wt%, significantly reducing the inhibition costs.<sup>2</sup> Generally the most successful kinetic hydrate inhibitors are polymers that contain small cyclic amides, particularly based on 5-membered (pyrrolidone) or 7-membered (caprolactam) rings (Scheme 1), either in the form of polyvinylcaprolactam (PVCap) and polyvinylpyrrolidone (PVP) or copolymers such as poly(VP/VCap), VC-713 and VIMA (*N*-methyl-*N*-vinylacetamide-vinylcaprolactam).<sup>2–4</sup> The global market for KHIs is substantial and includes major brands such as International Specialty Products (ISP) ‘Inhibex’ range of co-polymers based on vinyl caprolactam. Novel acryloyl pyrrolidine and isopropylacrylamide (IP) polymers have also recently been reported.<sup>5</sup> While there have been extensive studies on clathrate hydrate nucleation<sup>6</sup> and the mechanism of inhibition of hydrate formation by KHIs<sup>7–13</sup> including molecular dynamics studies based on VCap monomer<sup>14,15</sup> the process is not yet well understood. Vinyl caprolactam monomer, simulations suggest that the 7-membered ring backbone is included within the open face of a partially formed hexakaidecahedral cavity in the growing hydrate crystal.<sup>15</sup> Monomer-based studies, however, cannot directly address the effect of polymer steric requirements and cooperativity between adjacent lactam units. A recent MD simulation involving an 8-monomer PVP oligomer suggests significant interaction between the polar amide oxygen atoms and bulk water, although simulations of polymer in the presence of

crystalline methane structure I hydrate resulted in hydrate melting.<sup>16</sup> A two-step mechanism of KHI action has been proposed involving (a) disruption of local water order in liquid water by KHIs and (b) inhibitor binding to the growing crystal surface.<sup>15,16</sup> Other work conflicts with step ‘b’ and suggests that PVP increases interfacial surface energy without surface binding.<sup>17</sup> A further hypothesis emphasises kinetic factors.<sup>16</sup> We now report the synthesis of a small molecule model for PVCap containing two monomer repeat units, and present experimental, structural and DFT studies on its interaction with water. We show that this simple compound represents an appropriate model for commercial KHIs.

Reaction of VCap with trifluoroacetic acid under conditions reported<sup>18</sup> to dimerise the analogous VP results in the clean isolation of unsaturated dimer **1** in quantitative yield. Reduction to the saturated **2** can be achieved quantitatively using a ThalesNano H-Cube<sup>®</sup> Continuous-flow hydrogenation reactor. Both compounds have been reported previously in the patent literature with **2** used as a “solvent” for pharmaceutical or cosmetic compositions, although few details are given.<sup>19</sup> Compound **1** is crystalline and was characterised by X-ray crystallography.<sup>†</sup> The crystal packing was examined by Hirshfeld surface analysis<sup>20</sup> which showed the intermolecular interactions are dominated by CH...O hydrogen bonds to the polar carbonyl oxygen atom (Fig. 1a) which is expected to possess a significant partial negative charge in cyclic amides of this type (*ca.*  $-0.4^{21}$ ).

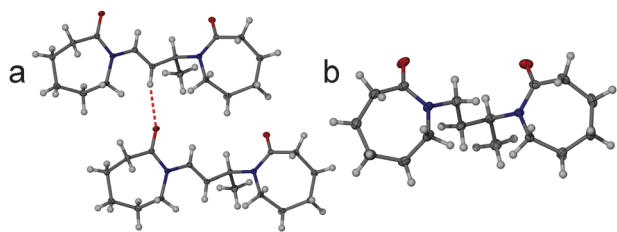
In contrast, **2** is isolated as a viscous oil. Rigorous drying of the compound under high vacuum does result in its crystallisation as a plastic solid (see the ESI<sup>†</sup>) however it is highly water soluble and on dissolution in water the oil re-forms. This high affinity of **2** for water may be linked to the behaviour of PVCap as a KHI and is likely to arise from the lack of strong



Scheme 1 Parent monomers, KHIs and model compounds.

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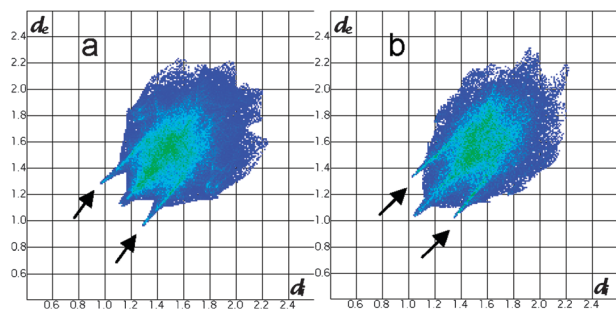


**Fig. 1** (a) X-Ray structure of **1** showing one of the strong CH...O interactions, (b) X-ray molecular structure of **2**.

hydrogen bond donor groups in **2** to match the strongly hydrogen bond basic oxygen atom. Crystalline **2** was characterised by synchrotron X-ray crystallography using beamline I19 at Diamond. The structure has a remarkably low density of  $1.162 \text{ g cm}^{-3}$  even at  $-123^\circ\text{C}$ , in contrast to **1** ( $1.231 \text{ g cm}^{-3}$ ) that seems linked to the very much weaker intermolecular interactions which comprise only very long CH...O contacts (Fig. 2) reflecting the low hydrogen bond acidity of the C(sp<sup>3</sup>)H groups. It is likely that this feature explains the highly hydrophilic nature of **2**, and hence PVCap.

The interaction of both **1** and **2** with water in comparison with a sample of commercial PVCap, and VCap and VP monomers was examined using IR and NMR spectroscopy. Previous IR spectroscopic studies on PVCap and PVP show that the frequency of the amide I band in a dry film of PVCap decreases on addition of up to 7 water molecules per monomer unit.<sup>21,22</sup> The amide I C=O stretching frequency for VP is significantly higher than VCap ( $1701 \text{ vs. } 1659 \text{ cm}^{-1}$ ) indicating more carbonyl double bond character in VP as a result of strain in the 5-membered ring. For VCap the less strained 7-membered ring results in a significantly greater contribution of the enolate resonance form and hence the VCap oxygen atom is expected to be a particularly good hydrogen bond acceptor. This difference is also reflected in data for PVP and PVCap,  $1685 \text{ vs. } 1640 \text{ cm}^{-1}$ .

IR spectroscopic measurements on **2** as a neat film show that the C=O stretch occurs at  $1628 \text{ cm}^{-1}$  close to the value for PVCap. The unsymmetrical **1** shows two C=O bands at  $1639$  and  $1622 \text{ cm}^{-1}$  in addition to an absorption at  $1667 \text{ cm}^{-1}$  assigned to the C=C stretching mode. The interaction of **1**, **2**, VP, VCap, PVCap and PVP with water was monitored by titration of D<sub>2</sub>O into a dry acetonitrile solution of the compounds. Acetonitrile was chosen because it possesses only weak hydrogen bond donor properties, while D<sub>2</sub>O was used instead of H<sub>2</sub>O



**Fig. 2** Hirshfeld surface fingerprint plots<sup>20</sup> (a) compound **1** showing CH...O interactions (arrows), (b) compound **2** in which the CH...O interactions are less pronounced.

because the OH bending mode in water obscures the carbonyl region of the IR spectra. In dry acetonitrile the C=O stretch in **2** occurs at  $1638 \text{ cm}^{-1}$  suggesting stronger hydrogen bonding to the carbonyl group in the neat film than in aprotic solution, consistent with the CH...O hydrogen bonding observed in the structure of **1**. As D<sub>2</sub>O is added in solution in aliquots up to 500 molar equivalents the C=O band broadens and shifts to  $1614 \text{ cm}^{-1}$  (see the ESI†). In pure D<sub>2</sub>O the band occurs at  $1609 \text{ cm}^{-1}$ . This data closely parallels the behaviour of commercial PVCap ( $1637 \text{ cm}^{-1}$  shifting to  $1614 \text{ cm}^{-1}$ ). Analogous titration of **1** results in a shift and broadening of the two carbonyl bands from  $1651$  and  $1632 \text{ cm}^{-1}$  to  $1636$  (shoulder) and  $1612 \text{ cm}^{-1}$ . This data show that both PVCap and the model compounds interact strongly with water, with hydrogen bonding to the polar carbonyl oxygen atom resulting in a weakening of the C=O bond. The behaviour of compound **2** in particular closely parallels the commercial polymer. Analogous titration with VP and PVP showed similar changes, which are summarised in Table 1.

Quantitative information regarding D<sub>2</sub>O binding by VP, VCap and compounds **1** and **2** was obtained by <sup>1</sup>H NMR spectroscopic titration in dry acetonitrile-*d*<sub>3</sub>. The resulting titration isotherms fit a combined 1 : 1 and 1 : 2 stoichiometric model for **1** and **2** while a 1 : 1 model was adopted for the monomers. Equilibrium constants were obtained by non-linear least squares regression using the program HypNMR. The resulting binding constants are given in Table 2. Overall, the binding constants are relatively weak. Compounds **1** and particularly **2** proved to bind a single water molecule somewhat more strongly than the monomers, although binding of the second water molecule is weak and shows no enhancement relative to the monomers. This data suggests that the dimeric model compounds may possess complementary water binding pockets. Binding constants for **2** may be underestimated due to the compound's hygroscopicity.

The structure of the stable solution monohydrate complex of **2** was probed by DFT calculations. The M06-2X functional from the Truhlar family was used, in conjunction with the 6-311(d,p) basis augmented by an extra set of diffuse s and p functions on the atoms involved in hydrogen bonding. Analytical Hessians were computed to confirm minima. The calculated structure of **2**·H<sub>2</sub>O is shown in Fig. 3 and reveals that **2** adopts a conformation that is highly complementary to water binding with the water guest molecule forming two, strong,

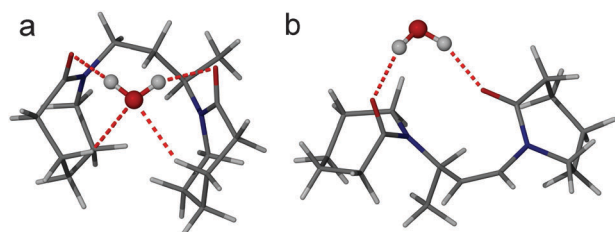
**Table 1** IR spectroscopic titration data for the amide I band in VP, VCap, **1**, **2**, PVP and PVCap with D<sub>2</sub>O (up to 500 molar equivalents) in dry acetonitrile solution

Compound	$\nu(\text{C=O}), \text{cm}^{-1}$		
	Neat	MeCN	MeCN + D <sub>2</sub> O
VP	1701	1704	1667
Vcap	1659	1662	1645
<b>1</b>	1639	1651	1636
	1622	1632	1612
<b>2</b>	1628/1625 <sup>a</sup>	1638	1614
PVP	1674/1685 <sup>b</sup>	1682	1654
PVCap	1621/1640 <sup>b</sup>	1637	1614

<sup>a</sup>  $1628\text{--}1630 \text{ cm}^{-1}$  as an oil,  $1625 \text{ cm}^{-1}$  as a crystalline solid. <sup>b</sup> Data from ref. 21 and 22.

**Table 2** Water binding constants determined by  $^1\text{H}$  NMR spectroscopic titration

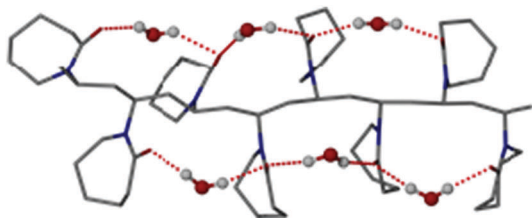
Compound	VCap	VP	1	2
$\text{Log}\beta_{11}$	-1.16(3)	-1.30(3)	-0.44(7)	0.24(3)
$K_{11}/\text{M}^{-1}$	0.07	0.05	0.36	1.74
$\text{Log}\beta_{12}$			-1.45(9)	-1.06(3)
$K_{12}/\text{M}^{-1}$			0.09	0.05

**Fig. 3** DFT calculated structure of (a)  $2\cdot\text{H}_2\text{O}$  showing pairwise  $\text{OH}\cdots\text{O}$  and  $\text{CH}\cdots\text{O}$  hydrogen bonds and (b)  $1\cdot\text{H}_2\text{O}$ .

symmetrical  $\text{OH}\cdots\text{O}$  interactions to the carbonyl groups while accepting  $\text{CH}\cdots\text{O}$  hydrogen bonds from the methylene groups of the VCap dimer receptor. The calculated structure of the monohydrate of **1** shows that the water molecule adopts a similar position in which it hydrogen bonds to both amide oxygen atoms, although the shape of **1** is less complementary to water and does not allow the formation of additional  $\text{CH}\cdots\text{O}$  interactions in the minimum energy geometry.

DFT calculations on dihydrates of **2** result in two structures of very similar energy, one involving the same motif as that shown in Fig. 3a with the second water molecule binding on the opposite side of one of the carbonyl groups. The other involves a directly water...water hydrogen bonded pair each forming only one  $\text{OH}\cdots\text{O}$  interaction to the inhibitor mimic. In each case complexation of the second water molecule would be expected to be less energetically favourable than the first.

In order to test whether such water-binding motifs are possible in PVCap, DFT calculations were carried out on short segments of syndiotactic polymer with 6–8 repeat units in the presence of varying numbers of water molecules. Water molecules were found to hydrogen bond between pairs of carbonyl oxygen atoms in a similar way to the model systems shown in Fig. 3. In the presence of a small number of water molecules each carbonyl group interacts with a single water molecule to give water situated between alternating VCap pairs. As the number of water molecules is increased the unoccupied sites are filled to give a water between every carbonyl pair (Fig. 4). Increasing the number of water molecules beyond the number of sites in between carbonyl pairs results in

**Fig. 4** DFT calculated structure of a 8-monomer segment of PVCap in the presence of six water molecules.

the development of water-water hydrogen bonded clusters spanning the gap between carbonyl pairs (see the ESI†). This bound water is likely to correlate with some of the *ca.* 6.5 molecules of non-freezable bound water per monomer unit in PVCap.<sup>23</sup>

In conclusion, IR data indicate that **2** behaves similarly to PVCap in its mode of interaction with water. The interaction is *via*  $\text{OH}\cdots\text{O}$  and  $\text{CH}\cdots\text{O}$  hydrogen bonding with **2** binding more strongly to water as a result of a unique complementary pocket that is likely to be a feature of commercial PVCap KHI. Structural studies reveal a very low density for **2** suggesting a lack of self-complementarity results in its very high hydrophilicity. The mode of action of PVCap as a KHI *via* hydrogen bond acceptance at the oxygen atoms may be related to the presence of ester carbonyls in acid impurities in non-plugging oils.<sup>24</sup>

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## Notes and references

- C. A. Koh, *Chem. Soc. Rev.*, 2002, **31**, 157.
- M. A. Kelland, *Energy Fuels*, 2006, **20**, 825.
- E. M. Freer and E. D. Sloan, in *Gas Hydrates: Challenges for the Future*, ed. G. D. Holder and P. R. Bishnoi, New York Acad. Sciences, New York, 2000, vol. 912, p. 651.
- J. P. Lederhos, J. P. Long, A. Sum, R. L. Christiansen and E. D. Sloan, *Chem. Eng. Sci.*, 1996, **51**, 1221.
- M. A. Kelland, T. M. Svartaas, J. Øvsthus, T. Namba, [http://www.uilrigg.no/internet/student.nsf/199f312efd2a0cacc125680e00635b85/b58dc01591e3feac125768f004f4a66/\\$FILE/Fagernes%20paper.pdf](http://www.uilrigg.no/internet/student.nsf/199f312efd2a0cacc125680e00635b85/b58dc01591e3feac125768f004f4a66/$FILE/Fagernes%20paper.pdf).
- M. R. Walsh, C. A. Koh, E. D. Sloan, A. K. Sum and D. T. Wu, *Science*, 2009, **326**, 1095.
- E. D. Sloan, S. Subramanian, P. N. Matthews, J. P. Lederhos and A. A. Khokhar, *Ind. Eng. Chem. Res.*, 1998, **37**, 3124.
- J. M. Cohen, P. F. Wolf and W. D. Young, *Energy Fuels*, 1998, **12**, 216.
- C. Lo, J. S. Zhang, P. Somasundaran, S. Lu, A. Couzis and J. W. Lee, *Langmuir*, 2008, **24**, 12723.
- J. S. Zhang, C. Lo, A. Couzis, P. Somasundaran, J. Wu and J. W. Lee, *J. Phys. Chem. C*, 2009, **113**, 17418.
- R. Larsen, C. A. Knight and E. D. Sloan, *Fluid Phase Equilib.*, 1998, **150**, 353.
- A. K. Sum, R. C. Burruss and E. D. Sloan, *J. Phys. Chem. B*, 1997, **101**, 7371.
- E. D. Sloan, S. Subramanian, P. N. Matthews, J. P. Lederhos and A. A. Khokhar, *Ind. Eng. Chem. Res.*, 1998, **37**, 3124.
- T. J. Carver, M. G. B. Drew and P. M. Rodger, *J. Chem. Soc., Faraday Trans.*, 1995, **91**, 3449.
- B. J. Anderson, J. W. Tester, G. P. Borghi and B. L. Trout, *J. Am. Chem. Soc.*, 2005, **127**, 17852.
- T. Kuznetsova, A. Sapronova, B. Kvamme, J. Johannsen and J. Haug, *Macromol. Symp.*, 2010, **287**, 168.
- C. Moon, R. W. Hawtin and P. M. Rodger, *Faraday Discuss.*, 2007, **136**, 367.
- J. C. Zhuo, *Molecules*, 1999, **4**, M117.
- USA Pat., US6497886, 2002.
- M. A. Spackman and D. Jayatilaka, *CrystEngComm*, 2009, **11**, 19.
- Y. E. Kirsh, N. A. Yanul and K. K. Kalninsk, *Eur. Polym. J.*, 1999, **35**, 305.
- Y. Maeda, T. Nakamura and I. Ikeda, *Macromolecules*, 2002, **35**, 217.
- M. Varma-Nair, C. A. Costello, K. S. Colle and H. E. King, *J. Appl. Polym. Sci.*, 2007, **103**, 2642.
- K. Erstad, S. Høiland, T. Barth and P. Fotland, "Isolation and Molecular Identification of Hydrate Surface Active Components in Petroleum Acid Fractions", *Proceedings of the 6th International Conference on Gas Hydrates*, 2008.